activity[, partial agonist activity,] or agonist activity to said receptor[.]; and

(c) directly identifying a compound of step (b) having inverse agonist activity as an inverse agonist to said receptor, or having agonist activity as an agonist to said receptor.

Please cancel claims 41-44, without prejudice.

II. In The Specification

Please delete Appendices A through D, inclusive, as filed, and kindly substitute re-numbered Appendices A through D, inclusive, as pages 77-87, inclusive (substitute pages attached hereto).

Kindly substitute the Sequence Listing (as amended to include the requested SEQ ID NO information of Figure 12) as pages 88-97, inclusive (substitute pages attached hereto).

Kindly re-number the "Claim" pages 88-91 by changing "88" to --98--; "89" to --99--; "90" to --100--; and "91" to --101--.

III. In The Drawings

Kindly substitute Figure 12 as filed with the attached amended Figure 12 (the amendment includes, as requested, an indication of the SEQ ID NO designations for "GPR3", "GPR6" and "GPR12".

B. RESPONSE

Applicants initially thank Examiner Basi for the time and attention accorded this case. Applicants confirm that the Office has received and made of record the Preliminary Amendments filed on October 14, 1999 and September 8, 1999. Applicants further note that the "First Supplemental IDS" filed October 2, 1998, has been made of record, and Applicants acknowledge receipt of the signed and dated Form 1449 corresponding to that IDS. It appears, however, based upon an inspection of the PTO file in this case, that the original IDS, filed July 13, 1998, may have been misplaced inadvertently by the Office in that Applicants have received a copy of the date-stamped return post card filed with the original IDS, but the IDS itself is apparently not a part of the PTO file. Thus, filed herewith is a copy of the IDS as filed in July of 1998, including the references and a copy of the date-stamped post-card. Applicants regret any inconvenience that this may cause the Examiner, and respectfully request that the references be entered into this case.[1]

[1] Applicants note that a reference in the July 1998 IDS, Eggerickxx, has been made of record via the First Supplemental IDS.

With respect to the Restriction Requirement, it is noted that Applicants restriction was made without traverse (for reasons set forth therein), and that, by this Response, Applicants have cancelled claims 19-32, 35-38 and 41-44, without prejudice, as being drawn to a non-elected invention – these claims will be pursued at a later date. As requested by the Office, Figure 12, which provides the amino acid sequences for "GPR3", "GPR6" and "GPR12", has been amended to include sequence listing identifiers, and this has necessitated an amendment to the Sequence Listing. Applicants further appreciate the level of detail that the Examiner has provided in the examination of the Specification and as a result thereof, Applicants have requested amendment to the Specification to re-order the positioning of Appendices A-D.

This is the first substantive examination of the claims in this case. Claims 1-18, 33-34 and 39-40 are pending. As will be discussed below, all pending claims have been rejected under the provisions of 35 USC Section 112, first paragraph and 35 USC Section 112, second paragraph.

The claimed invention is directed to a method for directly identifying candidate compounds as specified modulators of "orphan" receptors. As will be set forth below, Applicants assert that the claimed invention, as filed, and the claims, as filed and clarified, comply with the provisions of Section 112, first and second paragraphs.

I. Claim Rejection, 35 U.S.C. 112, Second Paragraph

Claims 1-18, 33-34 and 39-40 have been rejected under 35 USC 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

With respect to claims 1, 33 and 34 and the phrase "partial agonists," Applicants note that this phrase is fully defined in the Specification (page 17) with sufficient particularity as required under Section 112. However, the assignee of this application is a small, start-up organization whose ability to progress from a business perspective would be enhanced by issuance of this case such that, for this reason alone, Applicants have opted to expedite prosecution of this case by amending the claims to delete the phrase "partial agonists" from claims 1, 33 and 34; this subject matter shall be pursued at a later date by Applicants in a separately filed application deriving priority, *inter alia*, from this application.

In view of the foregoing, this portion of the rejection is rendered moot.

Claims 1, 33 and 39 were considered indefinite due to the phrase "compound efficacy", and a perceived difference between the preamble of the claims and the claim steps. Focusing on the later issue first, claims 1, 33 and 39 have been amended to include a "candidate identification" step as suggested by the Office, and to clarify the orphan receptor portion of the claim. Applicants note, for the record, that an "orphan receptor" can be a "constitutively activated orphan receptor" (*e.g.*, an endogenous orphan receptor can be constitutively active), and, *e.g.*, an inverse agonist identified in accordance with

the claims using a constitutively activated version of the orphan receptor is desirably expected to evidence the same activity against the endogenous orphan receptor. The purpose of the constitutively active orphan receptor in the context of the claimed invention is to establish a "signal" that can be assessed in the absence of endogenous ligand-binding; this allows for "screening" of the receptor to directly identify modulators of the receptor, as evidenced by changes in the signal. These clarifications are not believed to adjust the scope of the claims as filed, and indeed have been made to further clarify, from a linguistic perspective, the claim structure. Applicants respectfully submit that in view of the amendments, this portion of the rejection is rendered moot.

With respect to the phrase "compound efficacy" the Office notes the following:

> "Claims 1, 33 and 39 are indefinite because it is unclear what is 'compound efficacy' and what parameters are measured to determine said efficacy so as to allow metes and bounds of the claims to be determined."

On this point, Applicants note that the phrase "compound efficacy" is defined in the Specification on page 18 as follows:

> "COMPOUND EFFICACY shall mean a measurement of the ability of a compound to inhibit or stimulate receptor functionality, as opposed to receptor binding affinity. A most preferred means of detecting compound efficacy is via measurement of [^{35}S]GTPγS binding, as further disclosed in the Examples section of this patent document."

In the Table of Contents filed with this application, Section III is entitled, "Use Of Second Messenger Assays To Detect Compound Efficacy" and this section is divided into two parts, G Protein Coupled Receptors and Tyrosine Kinase Receptors. Section III provides eight exemplary approaches to ascertaining "compound efficacy" (these pages are attached hereto for convenience). In the "Description of Preferred Embodiments" section, page 33 of the Specification, the following is provided:

> "In Section 'C' (sic, "III") set out below, confirmation of the constitutive activity of the transfected receptor in the expression system is disclosed. A variety of second messenger screening assays can be employed to detect the receptor-mediated cellular response. The assay chosen primarily depends upon the type of receptor and the secondary pathway it activates. For example, for some G protein-coupled receptors an adenyl cyclase activated system would provide the appropriate assay. For other G protein-coupled receptors, a phospholipase C linked assay would be appropriate. Appropriate assays for tyrosine kinase and other receptors are available and known to those skilled in the art. Preferred assays are summarized below. *The assays of constitutively activated receptor activity not only demonstrate the functioning of the receptor activity, but they also provide a means to directly determine when the level of that activity has been decreased or increased. Thus, compounds which are inverse agonists would be expected to lower the observed*

basal level of activity while compounds which are agonists would be expected to increase the activity level above baseline." [Emphasis supplied]

Example 2 provides an example of the preferred method for assessment of compound efficacy, the [^{35}S]GTPγS assay. Example 3 provides another example of assessment of compound efficacy based upon a reporter-based (β-galactosidase) system. Example 4 provides an example of an actual screen using two orphan receptors, GPR3 (*see also* Figure 16) and GPR6 (*see also* Figure 17) where the compound efficacy is ascertained based upon the changes in the measured signal.

Applicants assert that the phrase "compound efficacy" is both defined and exemplified in sufficient detail to allow one of ordinary skill in the art to practice the claimed invention. Because an orphan receptor does not have, by definition, a corresponding endogenous ligand that is known, a traditional approach to drug discovery, *e.g.*, interference with endogenous ligand binding to the receptor, is not viable – thus, as is disclosed in the present case, the "signal" to be measured with an orphan receptor is not predicated upon "receptor binding affinity" for the endogenous ligand, but rather "receptor functionality" (*i.e.*, the signaling activity of the receptor in the absence of ligand binding), and modulation of receptor functionality by a candidate compound, in this case, is defined as compound efficacy. This is established by both written disclosure and experimental data within the Specification as filed.

With due respect, Applicants request that upon review of the position taken by the Office, in light of consideration of the foregoing, that this portion of the rejection be withdrawn. Applicants respectfully request that the rejection of claims 2, 34, 40, 14, 3-13 and 15-18 also be withdrawn upon reconsideration for the reasons noted above. Claim 14, it is noted, has been amended to define the single letter amino acid designations by their accepted names such that this portion of the rejection is rendered moot.

Applicants respectfully submit that based upon the foregoing, all issues raised by the Office with respect to the rejection under the second paragraph of Section 112 have been completely addressed, and that upon reconsideration, such rejections be withdrawn as either moot or overcome.

II. Claim Rejection, 35 U.S.C. 112, First Paragraph

Claims 1-18, 33-34 and 39-40 have been rejected under 36 USC Section 112, first paragraph, as allegedly containing subject matter which was not disclosed in such a way to enable one skilled in the art to which it pertains, or which it is most nearly connected, to make and/or use the invention. According to the Office:

"The specification does not reasonably provide enablement for a method for identifying a candidate compound as a compound having activity selected from the group consisting of inverse agonist activity, partial agonist activity and agonist activity, to an orphan receptor, non-endogenous constitutively activated G protein

coupled cell surface orphan receptor or endogenous constitutively activated G protein coupled cell surface orphan receptor."

In support of this position (referred to herein as "Position A"), the Office notes the following:

> "The specification suggests strategies to convert G protein coupled receptors to become constitutively active after amino acid mutations but provides no examples of orphan receptors which have been converted to constitutively active forms after using said strategies."[2]

In further support of this position (referred to herein as "Position B"), and with focus on Watson (Ref A), the Office notes the following:

> "Therefore the disclosure of Watson predicts, using the primary structure of the orphan receptor the skilled artisan cannot predict its associated G-protein. Instant disclosure provides no information on determining specific G protein/orphan receptor complexes."

Finally, and in further support of this position (referred to herein as "Position C"), and with focus on Rudinger (Ref B), the Office notes the following:

> "Therefore, the lack of guidance provided in the specification and art as to the effects of specific mutations on specific orphan receptors that lead to constitutive activation of said orphan receptors, the unpredictability in the art of said mutations as disclosed above, what minimal requirements are necessary for said function, the lack of known binding partners of said receptors (G proteins), would prevent the skilled artisan from practicing the claimed invention without undue experimentation."

As will be addressed below, the claimed invention, as filed, fully complies with requirements of the first paragraph of Section 112. In support of this conclusion, Applicants shall refer to the Specification as filed, the claims as filed, and the attached "Declaration of Chen Liaw, Ph.D." (referred to herein as "Liaw Decla.").

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[2] On this point, applicants note that Example 4 provides data for screening of an endogenous, constitutively activated orphan receptor (GPR3 and GPR6) for the direct identification of compounds having inverse agonist activity to the receptors (see also Figures 16 and 17, respectively) such that Applicants assume that the basis of the rejection is limited only to orphan receptors that are not constitutively active in their endogenous form, but rather are constitutively active in their non-endogenous forms. If this assumption is incorrect, Applicants request clarification in the next communication from the Office.

A. Response to Office Position A

Position A: *The specification suggests strategies to convert G protein coupled receptors to become constitutively active after amino acid mutations but provides no examples of orphan receptors which have been converted to constitutively active forms after using said strategies*

As the Office will admit, it is not per se necessary to disclose an actual reduction to practice in order to comply with Section 112; the analysis is based upon the sufficiency of the disclosure, considered in the context of the skill level in the art. Here, with due respect, the view taken by the Office in Position A is accurate in terms of a specific example, but legally incorrect as to the impact of this under a Section 112 review.

Indeed, Section I of the Specification, pages 35 through 52, provide a variety of exemplary (non-limiting) approaches to achieving constitutive activation of a receptor, expression of the receptor (pages 53-54), assessment of the activity of the receptor (pages 54-59), and methods for using these receptors for screening of candidate compounds (pages 59-63). With respect to what approach to utilize in an effort to establish constitutive activity of an orphan receptor, Applicants note the following on page 32 of the Specification:

> "In Section 'A' (sic, "I") set out below, a number of approaches to constitutively activating receptors are set forth. These approaches are based upon a detailed analysis and synthesis of the naturally occurring activation patterns which have been observed. *No single approach is a most preferred approach for any given receptor, in that, based upon the disclosure of this invention, these approaches provide the skilled artisan the opportunity to select, without undue experimentation and predicated upon the needs of the artisan, one or more approaches which will lead to a constitutively activated form of a given receptor.* [Emphasis supplied]

Thus, the purpose of the specification, under Section 112, is to provide guidance to the artisan whom, upon review of the specification, and using the skill-set of that artisan, can practice the claimed invention. In this context, attention is directed to pages 43-44 of the Specification, and the Liaw Decla. Pages 43-44 of the Specification deal with one example of an approach to mutation of a G protein coupled receptor. For presentational efficiency, these pages are reproduced below:

> "d. Universal Mutational Alignment
>
> "The C terminal region of the third intracellular loop adjacent to transmembrane section six has been shown to be important for G protein coupling. In the $\alpha 1\beta$-adrenergic receptor, substitution of any of the other 19 amino acids for alanine 293 resulted in constitutive activation. Substitution with either glutamic acid or lysine resulted in the highest levels of constitutive activation. The cassette is as follows:

"EKKA (A at position 293 is substituted in the α1β-adrenergic receptor)

"The importance of this position is further substantiated by an analysis of a mutational data-base of the amino acid sequence alignment of all mutations which have been performed at this site and which have resulted in constitutive activation.

"A list of amino acid substitutions corresponding to position 293 of the α1β-adrenergic receptor which result in constitutive activation of the receptor are as follows:

(1) α1β-adrenergic receptor A293X where X is all remaining amino acids (Kjelsberg et al. 1992).
(2) Alpha 2A-adrenergic receptor T373(A, C, E, K, F) (Ren et al. 1993).
(3) Beta 2A-adrenergic receptor L272(A,I,T) (Pei et al. 1994).
(4) LH/CG receptor A568V (Latronico et al. 1995).
(5) TSH receptor A623I (Parma et al. 1993).
(6) Serotonin 5HT2A C322K (Casey et al. 1996)
(7) Serotonin 5-HT2C S312K/F (Barker et al. 1994; Herrick-Davis, 1996).
(8) Platelet-activating factor receptor L231R (Parent et al. 1996).
(9) Muscarinic m2 receptor (T386A) (Blin et al. 1995)

"Thus, it appears that changing the amino acid in this position to any other amino acid favors constitutive activation, but preferably the change is to a basic or acidic amino acid or another hydrophobic amino acid with differing side chains.

"If the 4 amino acid α1β-adrenergic receptor sequence is examined, another key position appears to be the acidic glutamic acid residue before the double basic residues, as follows:

EKKAA

"Mutation of amino acids which align to this position also results in constitutive activation across a number of receptor types as listed below:

(1) Beta2-adrenergic receptor E268G (O'Dowd et al. 1988).
(2) Muscarinic M1 receptor E360A (Hogger et al. 1995).
(3) LH/CGR receptor D564G (Laue et al. 1995).
(4) TSH receptor D619(G) (Parma et al. 1993)

"The amino acid motif represented by EKKAA is conserved to some extent in practically all G protein coupled receptors. For example, the double basic KK may be replaced by XK or RR or KR or RK (where X = any other amino acid).

"Based on these alignment observations across a variety of different classes of G protein-coupled receptors, an overall mutational insertion cassette is disclosed which

will have a general utility in constitutively activating G protein-coupled receptors. Due to the length differences between different G protein-coupled receptors, the numeric position (amino acid number) for cassette insertion will vary. *However, the point of insertion is 'positional' i.e., the point of insertion is at the junction of the third intracellular loop and transmembrane section six.*

"This cassette is:

$$X_1BBHyX_2$$

"where X_1 can be any amino acid, preferably G, A or K; where B is a basic amino acid; Hy is a hydrophobic amino acid, preferably A; X_2 is any amino acid, preferably K, R, E or a hydrophobic amino acid with a differing side chain to the original hydrophobic amino acid in that position. As further embodiments of this invention, this universal mutational cassette is most preferably utilized at the junction of the third intracellular loop and transmembrane section six to constitutively activate G protein-coupled receptors." [Emphasis supplied].

For convenience, the above-referenced single-letter amino acid codes correspond to the following amino acid residues: G = glycine; A = alanine; K = lycine; R = arganine; and E = glutamic acid.

It is noted that the "universal mutational cassette" is not the only approach disclosed in the Specification, but for purposes of addressing the broad point raised by the Office, this example is considered responsive[3]. Indeed, a variety of approaches can be used to mutate orphan receptors and achieve constitute activation thereof. The quoted section discloses and teaches an approach to establishment of constitutive activation. Attention is directed to the Liaw Decla. wherein Dr. Liaw declares to the following:

1) She has reviewed the Specification (Liaw Decla., ¶2);
2) Using commercially available software (DNA Star™), the amino acid residues located at and near the junction between the third intracellular loop (IC3) and transmembrane section six (TM6) of the receptor can be determined,(Liaw Decla., ¶3);
3) Using the aforementioned software, the location of the IC3/TM6 junction for the orphan G protein coupled receptors TDAG8 and GPR35, were determined; the amino acid at this junction for TDAG8 is Ile at position 225, and for GPR35, this amino acid is Ala at position 216 (Liaw Decla., ¶ 5);
4) As an approach for assessment of constitutive activation of TDAG8 and GPR35, the universal mutational cassette (X_1BBHyX_2) technique was analyzed on the TDAG8 and GPR35 receptors, such that the endogenous amino acid Ile in TDAG8, corresponding to

[3] Indeed, Applicants note that they are not, in this patent document, claiming mutated receptors as composition of matter, but rather the use of constitutively activated orphan receptors (whether endogenous or by mutation) to directly identify candidate compounds as modulators of the receptor.

position X_2 (at the IC3/TM6 junction position), was changed from Ile to K (Lys), and the endogenous amino acid Ala in GPR35, corresponding to position X_2 (at the IC3/TM6 junction position), was changed from Ala to K (Lys) (Liaw Decla.; ¶ 6);

5) Using a cyclic AMP, whole cell assay, the non-endogenous version of the TDAG8 receptor was determined to be constitutively activated, as evidenced by comparison between the endogenous-form signal and the comparative-increase in the non-endogenous form signal. Using a reporter-based assay (E2F-luciferase), the non-endogenous version of the GPR35 receptor was determined to be constitutively activated, as evidenced by comparison between the endogenous-form signal and the comparative-increase in the non-endogenous form signal (Liaw Decla., ¶7);

6) In her opinion, based upon these signals, the non-endogenous forms of the orphan receptors TDAG8 and GPR35 are viable for use in the direct identification of candidate compounds having inverse agonist activity or agonist activity at these receptors (Liaw Decla., ¶ 8).

In summary, using the information provided in the Specification as filed, commercially available reagents and assays, and ordinary skill, creation of a constitutively activated form of an orphan receptor is viable. In view of the foregoing, Applicants respectfully request that Position A be withdrawn upon reconsideration.

B. Office Position B

Position B: *Therefore the disclosure of Watson predicts, using the primary structure of the orphan receptor the skilled artisan cannot predict its associated G-protein. Instant disclosure provides no information on determining specific G protein/orphan receptor complexes.*

It is not *per se* necessary to identify the G protein that interacts with the receptor, as the Office implies. The Watson reference, as best understood in the context of the claimed invention, is not dispositive – this reference is believed to be directed to identification of sites within the G protein coupled receptor that bind to the G protein in an effort to determine *G protein specificity*. With due respect, this is not relevant to the issue at hand.

Indeed, a preferred assay as disclosed in the Specification is based upon measurement of GTP activity. This assay does not require knowledge of the G protein that binds to an activated receptor – whatever the G protein for a given receptor may be, when it binds to the receptor, the binding of GTP to the G protein is stimulated, and this reaction can be analyzed without knowledge of the primary G protein that binds with the activated receptor. As noted in Example 2:

> "When a G protein-coupled receptor is in its active state, either as a result of ligand binding or constitutive activation, the receptor binds to a membrane protein (called a G protein) and stimulates the binding of GTP to the G protein. The trimeric G protein-receptor complex acts as a GTPase and slowly hydrolyzes the GTP to GDP, at which point the receptor normally is deactivated. However, constitutively activated receptors continue to exchange GDP for GTP. The non-hydrolyzable GTP analog, [^{35}S]GTPγS, can be utilized to demonstrate enhanced binding of [^{35}S]GTPγS to membranes expressing constitutively activated receptors. Assays measuring [^{35}S]GTPγS binding are shown to confirm constitutive activation of the mutated human serotonin 5-HT$_{2C}$ receptor. The advantage of using [^{35}S]GTPγS binding to measure constitutive activation is that: (a) it is generically applicable to all G protein- coupled receptors; (b) it is proximal at the membrane surface making it less likely to pick-up molecules which affect the intracellular cascade.
>
> "The assay utilizes the ability of G protein coupled receptors to stimulate [^{35}S]GTPγS binding to membranes expressing the relevant receptors. The assay can, therefore, be used in the direct identification method to screen candidate compounds to known, orphan and constitutively activated G protein coupled receptors. *The assay is generic and has application to drug discovery at all G protein coupled receptors*." [Emphasis supplied].

Furthermore, the skilled artisan would be expected to understand that the G protein can be surmised based upon the assessment of signal response from the assay utilized. For example, prior to the filing date, it was known that the binding of the G protein Gs to the receptor stimulates the production of adenyl cyclase, while the binding of the G protein Gi to the receptor inhibits the production of adenyl cyclase. Thus, if an assay based upon cyclic AMP is utilized (as was the case for TDAG8, discussed above), an increase in the cAMP signal indicates that the primary G protein associated with the binding to the receptor can be Gs; when the signal is reduced upon constitutive activation (*e.g.*, below the baseline signal of the endogenous, non-constitutively activated receptor), this would indicate that the primary G protein associated with the binding to the receptor can be Gi.[4] Other assay systems known in the art can similarly be used to gain, if desired, an understanding of the primary G protein that binds to the receptor.

Thus, and while not accepting the premise drawn by the Office with respect to Point B, Applicants note that in response to this position, it is not necessary to understand the G protein in order to practice the claimed invention.

In view of the foregoing, Applicants respectfully request that upon reconsideration, Position B be withdrawn.

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[4] See, for example, Chpt 8, "Indirect Mechanisms of Synaptic Transmission" in From Neuron to Brain, 3rd ed., Nichols, J.C et al, eds. Sinauer Associates, Inc. 1992. A copy of Chapter 8 is attached.
For convenience on the point, please refer to page 248.

C. Office Position C

Position C: *Therefore, the lack of guidance provided in the specification and art as to the effects of specific mutations on specific orphan receptors that lead to constitutive activation of said orphan receptors, the unpredictability in the art of said mutations as disclosed above, what minimal requirements are necessary for said function, the lack of known binding partners of said receptors (G proteins), would prevent the skilled artisan from practicing the claimed invention without undue experimentation.*

With due respect to the reference cited by the Office, the examples provided above with respect to the orphan receptors TDAG8 and GPR35, and the numerous assay examples provided in the Specification, including the [^{35}S]GTPγS assay which does not require knowledge of the G protein that binds with the receptor, fairly calls into question the breadth of the conclusion drawn from the reference. As such, Applicants respectfully request that upon reconsideration, Position C be withdrawn by the Office.

D. Summary

A purpose of Section 112, first paragraph is to ensure that one of ordinary skill in the art, upon review of the disclosure, is able to practice the claimed invention without undue experimentation. The law makes clear that some experimentation is acceptable, so long as it is not "undue." Claims 1-18, 33-34 and 39-40 were rejected based upon an allegation of non-compliance with Section 112, first paragraph. With due respect, the points raised and discussed above in response to the points asserted by the Office allow for a conclusion that upon reconsideration, this rejection must be withdrawn. Such an outcome is warranted, and therefore respectfully requested by Applicants.

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III. Conclusion:
Claims 1-18, 33-34 and 39-40 Are In Condition For Allowance

This is the first substantive examination of the claims in this case. Claims 1-18, 33-34 and 39-40 are pending. By this Response, claims 1, 14, 33 and 39 have been amended, and claims 19-32, 35-38 and 41-44 have been cancelled, without prejudice, as being drawn to a non-elected invention. Claims 1-18, 33-34 and 39-40 were rejected under 25 USC Section 112, first and second paragraph; no claim was rejected under any provision of Section 102 or 103. As set forth above, and with reference to the Declaration of Chen Liaw, Applicants respectfully submit that they have fully addressed and cogently overcome the positions taken by the Office in support of the rejections. Thus, Applicants request that the rejections be withdrawn upon reconsideration. Applicants further request that a Notice of Allowance issue in this case in due course. To the extent that Examiner Basi wishes to discuss any aspect of the above, or any aspect related to this case, he is kindly invited to contact Ms. Nguyen or Mr. Burgoon at the number listed below.

Respectfully submitted,

Dated: Feb 15, 2000

By: _____
Ann Nguyen
Reg. No. P-46,087

Dated: Feb 15, 2000

By: _____
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